REMARKS/ARGUMENTS

The Pending Claims

Claims 1, 3, 6, 8, and 11-33 are pending and are directed to 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid ("DOTA") compounds of formula (I), (II), and (III), complexes thereof, compositions thereof, methods of use thereof, and conjugates thereof.

Amendments to the Specification and Claims

The specification has been amended to identify the trademarked product HERCEPTIN™. The trademark symbol "™" has been placed on the first occurrence at paragraph [0019]. It is not necessary to place the symbol at subsequent occurrences, such as the footnote of page 33. All occurrences of HERCEPTIN have been capitalized.

Claims 6, 8, 26, and 33 have been rewritten in independent form. Claims 11, 12, 19, 21, 23, and 23 have been amended to clarify that the moieties are metal ions, as supported by the specification at, for example, paragraphs [0045] and [0046]. Claim 17 has been amended to recite Gd(III), as supported by the specification at, for example, paragraph [0045].

No new matter has been added by way of these amendments.

Summary of the Office Action

The Office objects to the specification. In addition, the Office objects to claim 17. Claims 1, 3, 6, 8, and 11-33 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. Claims 15, 16, 18, 20, 22, and 29-33 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1, 6, 11, and 13 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Moi et al. (*J. Am. Chem. Soc.*, 110: 6266-6267 (1988)) in view of U.S. Patent 5,049,667 (Schaefer et al.). Claims 1, 3, 6, 8, 11-19, and 28-30 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over of Moi et al. in view of U.S. Patent 5,358,704 (Desreux et al.). Claims 20 and 21 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Moi et al., Schaefer et al., and Desreux et al. in view of U.S. Patent 5,428,156 (Mease et al.). Finally, claims 22-27 and 31-33 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable

over Moi et al., Schaefer et al., and Desreux et al. in view of U.S. Patent 5,428,154 (Gansow et al.). Reconsideration of the pending claims is hereby requested.

Discussion of the Objection to the Specification

Applicants have amended the specification as discussed. In view of the amendment, the objection to the specification has been overcome.

Discussion of the Claim Objection

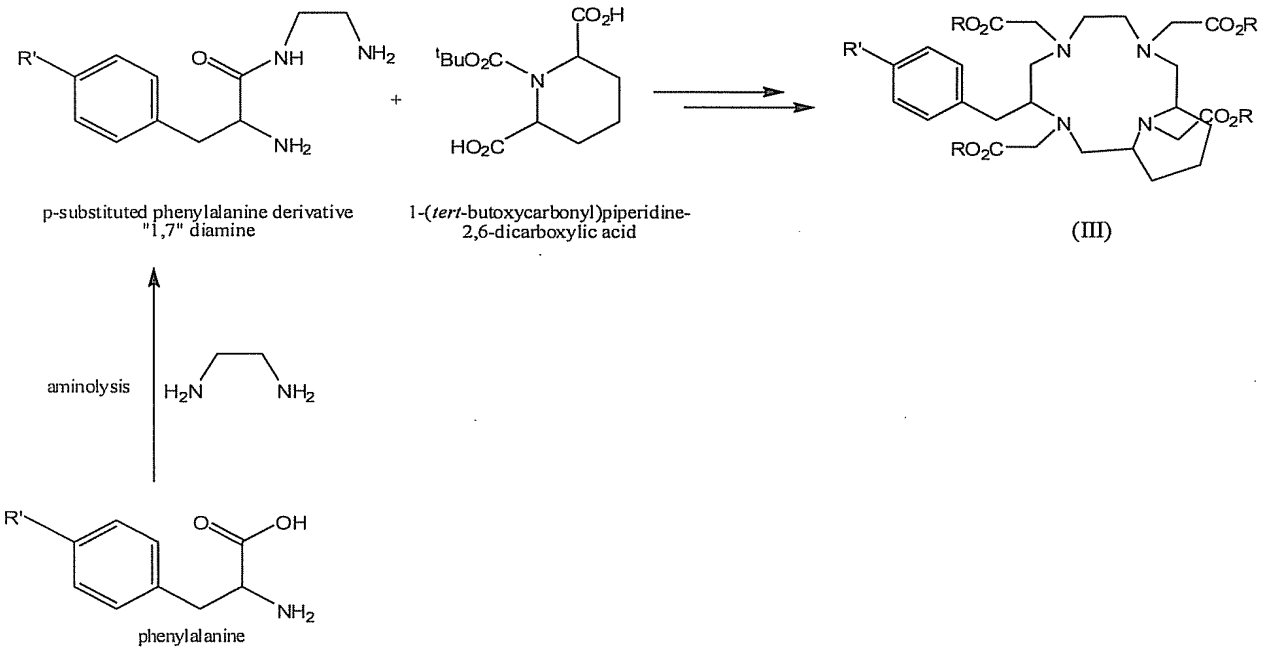
The Office objects to claim 17 since the claim refers to a metal ion. As suggested by the Office, claim 17 has been amended to recite the metal ion Gd(III). In view of this amendment, it is submitted that the claim objection has been overcome.

Discussion of the Enablement Rejection

Claims 1, 3, 6, 8, and 11-33 allegedly lack enablement by the specification. Specifically, the Office contends that the specification is enabling for compounds of formula (I) and (II) but does not reasonably provide enablement for the compound of formula (III). The Office alleges that it would involve undue experimentation to prepare and use compounds of formula (III). Applicants respectfully disagree.

The specification adequately describes how to prepare compounds of formulas (I)-(III) (see, for example, paragraph [0040]). For instance, the specification describes that the synthesis of a compound of formula (I) is initiated from a derivative of p-substituted-phenylalanine. The p-substituted phenylalanine derivative ("1,7" diamine) can be either purchased commercially or synthesized via, for example, aminolysis of 1,2-diaminoethane and p-substituted phenylalanine. The "1,7" diamine is reacted with a bis(succinimidyl)ester of BOC-iminodiacetic acid. The specification also teaches that the "strategy can be directly applied to construct a wide range of macrocyclic rings by using functionalized amines (e.g., alkyl substituted, aryl substituted, heteroaryl substituted, cycloalkyl substituted; etc.). *This is equally the case for the other cyclization component.*" (paragraph [0040], lines 2-8, emphasis added). By following the above guidelines, one of ordinary skill in the art can prepare compounds of formula (III) without undue experimentation.

Similarly, compounds of formula (III) can be prepared based on the description of preparing compounds of formula (II) (e.g., Examples 7-14). For example, one of ordinary skill in the art could make suitable modifications to the phenylalanine derivative and BOC-iminodiacetic acid disuccinimidyl ester used Example 7. Based on the above, those of ordinary skill in the art can prepare compounds of formula (III), for example, by the following method:



The specification further provides reaction conditions, such that the cyclization typically occurs under relatively high-dilution conditions with equimolar addition controlled by addition of the two components via syringe pump (paragraph [0040], line 6-8). Moreover, the specification describes that the requisite substituted diamines and subsequent substituted phenylalanines are readily available from extensive literature and the host of possibilities associated with amino acids to provide not only desired substituents and the appropriate regiochemistry, but also to provide them in desirable stereochemistry. Additionally, the stereoselective introduction of substituents on the carboxylate functional groups is also readily available from routine, well-established amino acid chemistry (paragraph [0040], lines 9-17).

In addition to the above teaching, the specification also describes how to use a compound of formula (III). The specification further describes pharmaceutical compositions at, for example, paragraphs [0049]-[0055], which includes formulation, modes of administration, and dosing information. Methods of using a compound of formula (III) for diagnostic imaging and/or a therapeutic method are described at, for example, paragraphs [0056]-[0064]. Such methods include using a compound of formula (III) for a magnetic resonance image, an x-ray contrast image, single photon emission computed spectroscopy (SPECT) image, or for treating a cellular disorder. The specification further teaches that the compounds of formula (III) can be conjugated to a biomolecule. This process and examples of such conjugates are described in the specification at, for example, paragraphs [0041]-[0044]. Metal complexes of compounds of formula (III) can be prepared as described in the specification at, for example, paragraphs [0045]-[0048].

Some amount of experimentation, if required, is permissible under 35 U.S.C. § 112, first paragraph. The statute does not require a description detailed as a production manual. Thus, for example, varying time, temperature, solvents, and purification conditions are expected to be within the skill set of the artisan and are not required to be spelled out.

In view of the foregoing, Applicants respectfully submit that a person skilled in the art would be able to make and use the invention without undue experimentation. Accordingly, the rejection under Section 112, first paragraph should be withdrawn.

Discussion of the Indefiniteness Rejection

Claims 15, 16, 18, 20, 22, and 29-33 allegedly are indefinite. However, the remarks regarding indefiniteness are limited solely to claim 17 and its recitation of Gd as a metal ion. As discussed above, claim 17 has been amended to recite the metal ion Gd(III). In view of this amendment, the indefiniteness rejection has been overcome.

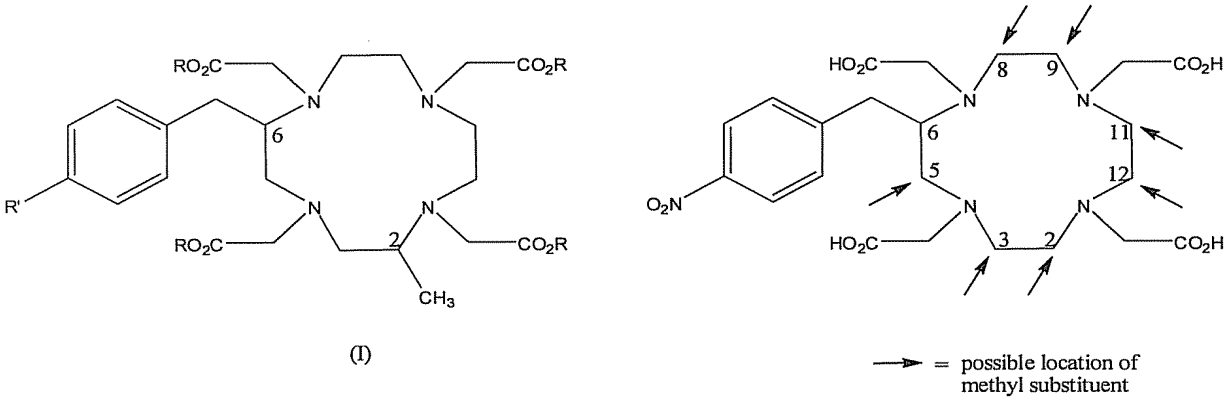
Discussion of the Obviousness Rejections

A. Moi et al. and Schaefer et al.

Claims 1, 6, 11, and 13 allegedly are obvious over Moi et al. in view of Schaefer et al. Moi et al. discloses p-nitrobenzyl-DOTA. Schaefer et al. discloses 2-methyl-DOTA.

According to the Office, it would have been obvious to combine the disclosures of Moi et al. and Schaefer et al. to arrive at a compound of formula (I). Applicants respectfully disagree.

As conceded by the Office, Moi et al. does not disclose a DOTA compound that has a methyl substituent on the backbone. Also as conceded by the Office, Schaefer et al. does not disclose a bifunctional DOTA compound having a p-nitrobenzyl substituent. The Office alleges, however, that it would have been obvious to combine the two disclosures to arrive at a compound of formula (I). Applicants respectfully submit that the Office has failed to make a *prima facie* case for obviousness, since no pointer is found in either reference that would lead one of ordinary skill in the art to arrive at the *exact* structure of formula (I) with its *exact* placement of substituents. Even if, for the sake of argument, that it was obvious to combine the teachings of Moi et al. and Schaefer et al., the ordinarily skilled artisan would have seven different backbone carbon atoms to choose from for placement of the methyl substituent relative to the p-nitrobenzyl substituent (see the following schematic).



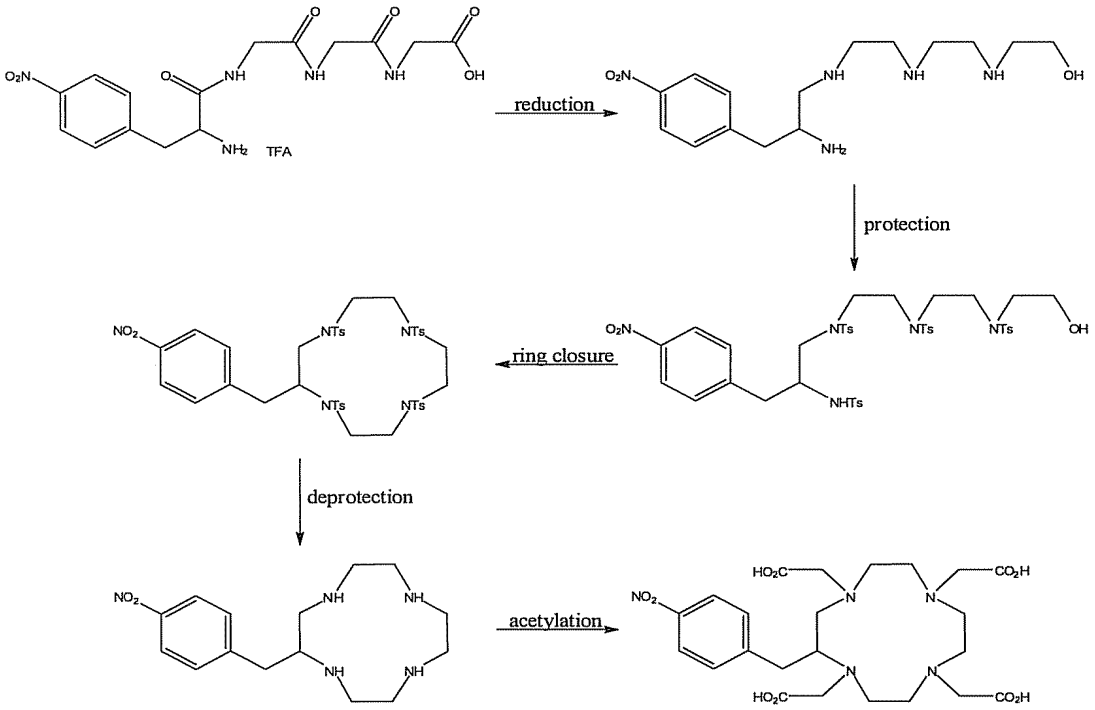
The compound of formula (I) has the methyl and p-nitrobenzyl substituents in a 2/6 relationship. Based on Moi et al. and Schaefer et al.'s disclosures, even if the Office is correct in combining them, the ordinarily skilled artisan would be equally led to provide DOTA compounds with substituents in a 2/6, 3/6, 5/6, 8/6, 9/6, 11/6, or 12/6 relationship. Specifically, there is no pointer or suggestion to place the methyl group at the 2-position. As a result, to contend that the compound of formula (I) is obvious based on the combination of Moi et al. and Schaefer et al. surmounts to the impermissible use of hindsight. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat

patentability, this amounts to nothing more than impermissible hindsight." *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617. (Fed. Cir. 1999).

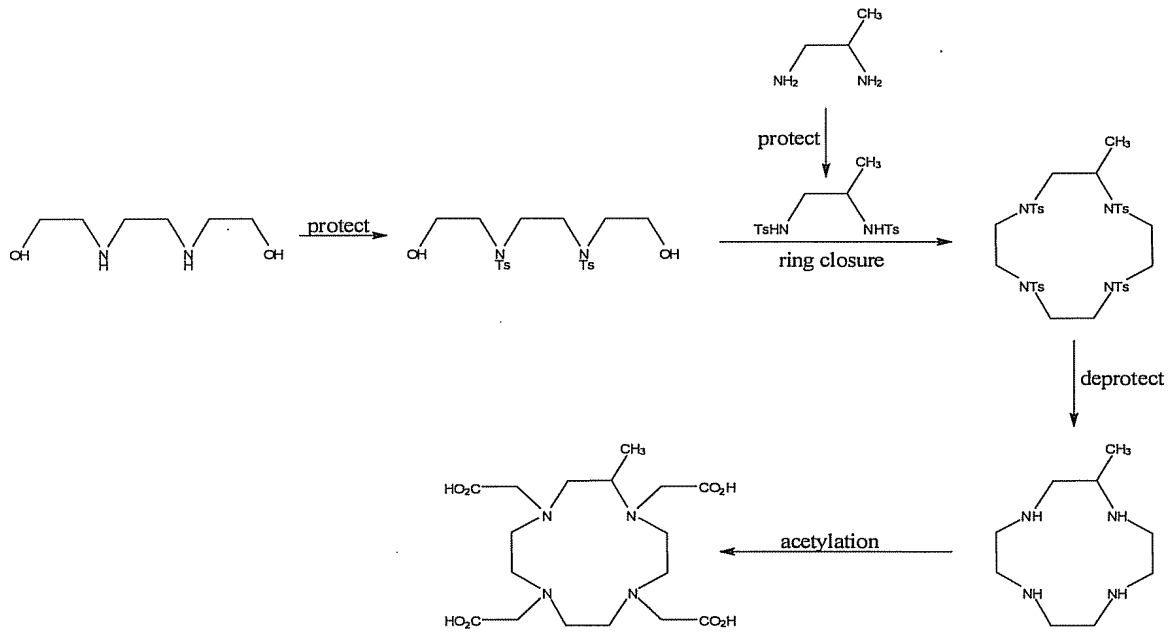
In *Takeda Chemical Industries, Ltd., et al. v. Alphapharm PTY., Ltd., et al.*, Case No. 06-1329 (Fed. Cir., June 28, 2007), the Federal Circuit held that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." Moreover, the Supreme court found that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR International Co. v. Teleflex Inc. et al.*, Case No. 04-1350 (April 30, 2007). In the present application, the burden is on the Office to show that a design need or market pressure exists in order to make a structural change. In the absence of this showing, as is the current situation, a *prima facie* case of obviousness has not been established. Here, the Office failed to identify a reason why one of ordinary skill in the art would want to place a methyl group at the 2-position. Based on the disclosures of Moi et al. and Schaefer et al., or any other cited reference for that matter, there is no specific design need or market pressure to place a methyl and p-nitrobenzyl substituents in a 2/6 relationship.

Moreover, the cited references fail to disclose a method for making the compound of formula (III). The syntheses of the DOTA compounds described by Moi et al. and Schaefer et al. are different from each other, and there is no clear path to a compound of formula (I). For instance, Moi et al. describes starting with a deprotected tetrapeptide and reducing it to a tetraamine. The tetraamine is protected and then ring closed. The protected ring is then deprotected, and the acetate functionality is added. In constrast, Schaefer et al. describes forming two protected diamines and combining and ring closing them. The protected ring is then deprotected, and the acetate functionality is added. See the following reaction schemes.

Moi et al.



Schaefer et al.



The two syntheses cannot be combined by one of ordinary skill in the art into a single synthesis to prepare a compound of formula (I). Therefore, there is no reasonable expectation of success in arriving at the claimed invention. Emphasizing this point is the fact that Applicants developed a different and novel synthesis to prepare a compound of formula (I). See, for

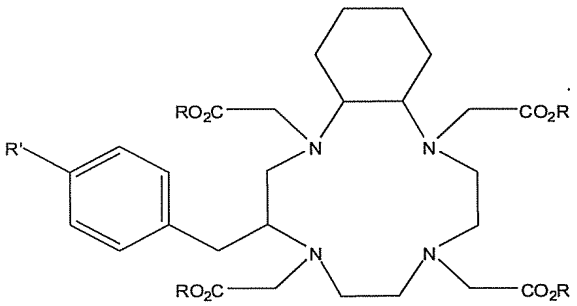
example, paragraph [0040], Examples 1-6, and Figure 1 of the instant specification. The syntheses described in Examples 1-6 differ from the disclosures of both Moi et al. and Schaefer et al. Where the prior art fails to disclose or suggest a method for making the claimed compound, the compound cannot be obvious over the art. See, e.g., *In re Hoeksema*, 158 U.S.P.Q. 596 (C.C.P.A. 1968).

In view of the foregoing, the Office has not met its burden to establish a *prima facie* case of obviousness. Accordingly, the obviousness rejection of claims 1, 6, 11, and 13 should be withdrawn.

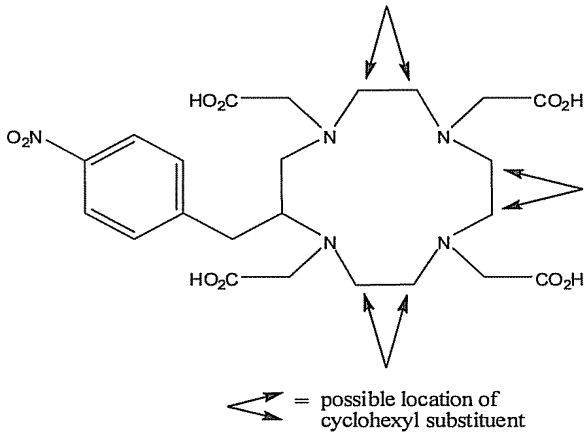
B. Moi et al. and Desreux et al.

Claims 1, 3, 6, 8, 11-19, and 28-30 allegedly are obvious over Moi et al. in view of Desreux et al. Moi et al. discloses p-nitrobenzyl-DOTA. Desreux et al. discloses cyclohexyl backbone-substituted-DOTA. According to the Office, it would have been obvious to combine the disclosures of Moi et al. and Desreux et al. to arrive at a compound of formula (II).

Moi et al. does not disclose a DOTA compound that has a cyclohexyl substituent on the backbone. Desreux et al. does not disclose a bifunctional DOTA compound that comprises a benzyl substituent that can conjugate to a biomolecule. It allegedly would have been obvious to combine the two disclosures to prepare a compound of formula (II), yet the Office has failed to present a *prima facie* case of obviousness. In particular, nothing in either reference would lead one of ordinary skill in the art to arrive at the *exact* structure of formula (II) with its *exact* placement of substituents. As with the compound of formula (I), discussed above, more than one possibility exists for providing compounds with both a benzyl substituent and a cyclohexyl substituent (see the following schematic).



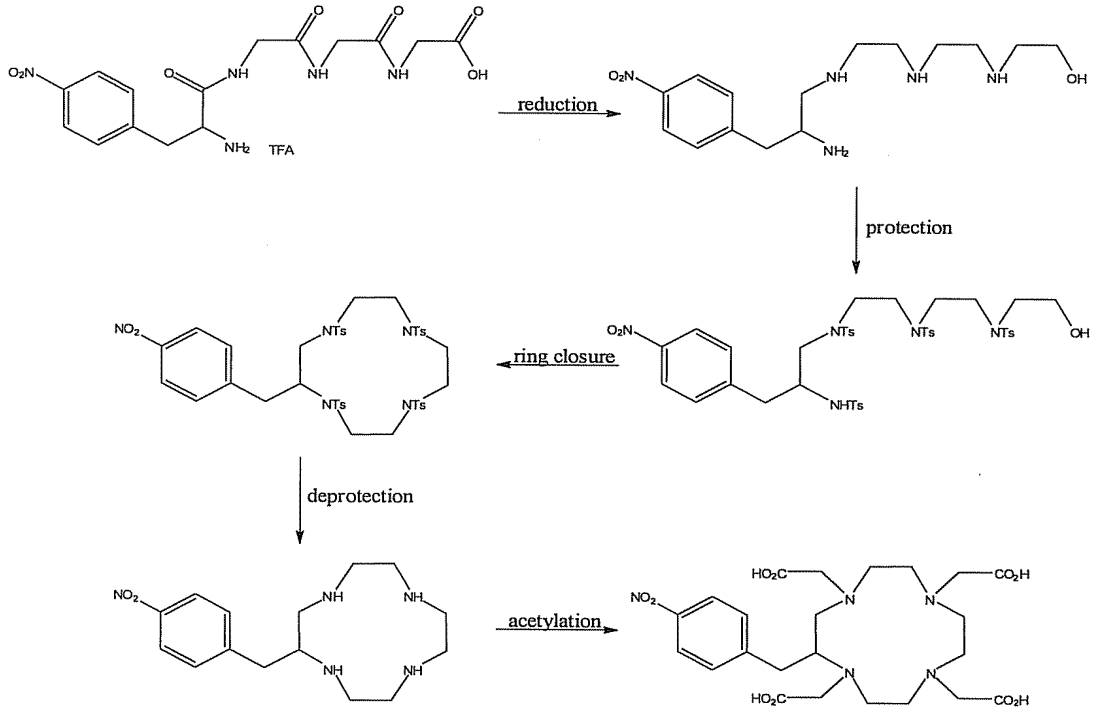
(II)



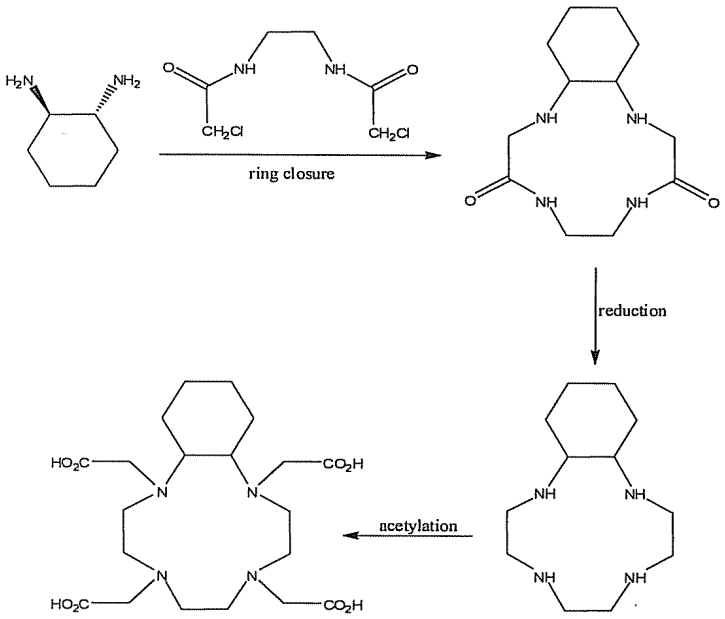
Since the Office has failed to identify some reason that would have led a chemist to modify the compound of Moi et al. or Desreux et al. in a *particular* manner to arrive at the *precise* compound of formula (II), *prima facie* obviousness has not been established.

Again, as in the case of Moi et al. and Schaefer et al., the syntheses of the DOTA compounds in Moi et al. and Desreux et al. are different enough, such that there is no clear route leading one to prepare the exact compound of formula (II). Moi et al. describes starting with a deprotected tetrapeptide and reducing it to a tetraamine. The tetraamine is protected and then ring closed. The protected ring is then deprotected, and the acetate functionality is added. Comparatively, Desreux et al. discloses combining two deprotected diamines and ring closing them. The ring is reduced, and the acetate functionality is added. No protection steps are taken. See the following reaction schemes.

Moi et al.



Desreux et al.



One of ordinary skill in the art would not be led to a synthesis route that provides the exact structure of the compound of formula (II). Accordingly, there is no reasonable expectation of success in arriving at the compound of formula (II). To prepare compounds of formula (II), Applicants had to develop a novel synthesis. See, for example, paragraph [0040], Examples 7-

14, and Figure 2 of the instant specification. The syntheses described in Examples 7-14 differ from the disclosures of both Moi et al. and Desreux et al. As discussed, where the prior art fails to disclose or suggest a method for making the claimed compound, an obviousness cannot exist. *Hoeksema.*

In view of the foregoing, the Office has not met its burden to establish a *prima facie* case of obviousness. Accordingly, the obviousness rejection of claims 1, 3, 6, 8, 11-19, and 28-30 should be withdrawn.

C. Moi et al., Schaefer et al., Desreux et al., and Mease et al.

Claims 20 and 21 allegedly are obvious over the combination of Moi et al. Schaefer et al., Desreux et al. and Mease et al. Moi et al. discloses p-nitrobenzyl-DOTA. Schaefer et al. discloses 2-methyl-DO TA. Desreux et al. discloses cyclohexyl backbone-substituted-DOTA. Mease et al. allegedly discloses a method of using a DOTA compound for SPECT imaging. According to the Office, it would have been obvious to combine the disclosures of the cited references to arrive at the subject matter of claims 20 and 21.

As discussed above, the combination of Moi et al. and either Schaefer et al. and Desreux et al. does not teach or suggest a compound of formula (I) or (II), as recited in the pending claims. Moreover, Mease et al. does not remedy the deficiencies of Moi et al., Schaefer et al., and Desreux et al. Specifically, Mease et al. does not teach or suggest the backbone-substituted bifunctional DOTA compound of formula (I) or (II). As such, the cited references do not recite all of the elements of claims 20 and 21, and the obviousness rejection in view thereof should be withdrawn.

D. Moi et al., Schaefer et al., Desreux et al., and Gansow et al.

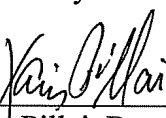
Claims 22-27 and 31-33 allegedly are obvious over the combination of Moi et al. Schaefer et al., Desreux et al. and Gansow et al. Moi et al. discloses p-nitrobenzyl-DOTA. Schaefer et al. discloses 2-methyl-DO TA. Desreux et al. discloses cyclohexyl backbone-substituted-DOTA. Gansow et al. allegedly discloses DOTA compounds conjugated to a biomolecule for treating a cellular disorder. According to the Office, it would have been obvious to combine the disclosures of the cited references to arrive at the subject matter of claims 22-27 and 31-33.

As discussed above, the combination of Moi et al. and either Schaefer et al. and Desreux et al. does not teach or suggest a compound of formula (I) or (II), as recited in the pending claims. Further, Gansow et al. does not cure the deficiencies of Moi et al., Schaefer et al., and Desreux et al. Gansow et al. does not teach or suggest the backbone-substituted bifunctional DOTA compound of formula (I) or (II). As such, the cited references do not recite all of the elements of claims 22-27 and 31-33, and the obviousness rejection in view thereof should be withdrawn.

Conclusion

A favorable decision is solicited. If, in the opinion of the Office, a telephone conference would expedite the prosecution of the subject application, the Office is invited to call the undersigned attorney.

Respectfully submitted,



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